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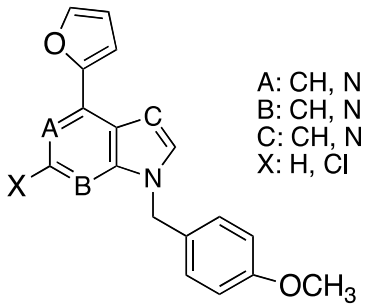

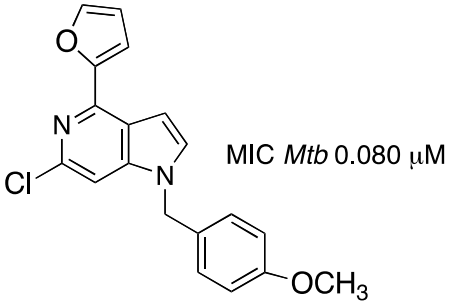

MIC *Mtb* 0.080 μM

Synthesis and antimycobacterial activities of non-purine analogs of 6-aryl-9-benzylpurines; imidazopyridines, pyrrolopyridines, benzimidazoles and indoles

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Abstract. 6,9-Disubstituted purines and 7-deazapurines are known to be powerful inhibitors of *Mycobacterium tuberculosis* (*Mtb*) *in vitro*. Analogs modified in the 6-membered ring (imidazopyridines, pyrrolopyridines, benzimidazoles and indoles) were synthesized and evaluated as *Mtb* inhibitors. The targets were prepared by functionalization on the bicyclic heterocycle or from simple pyridines. The results reported herein, indicate that the purine N-1, but not N-3, is important for binding to the unknown target. The 3-deazapurines appears to be slightly more active compared to the parent purines and slightly less active than their 7-deazapurine isomers. Removal of both the purine N-3 and N-7 did not result in further enhanced antimycobacterial activity but the

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toxicity towards mammalian cells was increased. Both 3-deaza and 3,7-dideazapurines exhibited a modest activity against of the *Mtb* isolate in the state of non-replicating persistence.

Introduction

Tuberculosis (TB) claims approximately 2 million deaths pr. year worldwide and resistance to the drugs in use is a growing problem. Also agents that reduce the duration and complexity of the current therapy would have a major impact on the overall cure rate.[1] We have studied 6,9-disubstituted purines as potent inhibitors of *Mycobacterium tuberculosis* (*Mtb*) *in vitro*, for instance compounds **1a** and **1b** (Fig. 1).[2] Lately we have examined several classes of non-purine analogs, and identified the 7-deazapurines **1c** and **1d** as even more active antimycobacterials.[3e] These compounds are highly selective towards *Mtb* compared to other microorganisms, active against several drug resistant strains of *Mtb*, generally non-toxic towards mammalian cells, and able to affect *Mtb* inside macrophages.[2,3] We now report the synthesis and antimycobacterial activities for purine- or 7-deazapurine analogs modified in the 6-membered ring (general structure, see Fig. 1).

(Fig. 1)

The synthesis of 1-deazapurines **5** is shown in Scheme 1. 2-Chloropyridines **2**[4] were reacted with *p*-methoxybenzylamine to give compounds **3** in high yields. The reaction on the 2,6-dichloropyridine **3b** was highly regioselective and only minor amounts of the other possible regioisomer were observed. The nitropyridines **3** were efficiently reduced to diamines **4** and the latter were reacted with triethylorthoformate to give the targets **5**.

(Scheme 1)

The 3-deazapurine **7** was readily available by a Stille coupling to introduce the furyl substituent on the previously known structure **6**[5] as shown in Scheme 2.

(Scheme 2)

For the chlorinated 3-deazapurine **12** the pyridine **8**[6] was chosen as the starting point (Scheme 3). The amine **8** was N-alkylated with *p*-methoxybenzyl chloride, and the furyl group was introduced

by a highly regioselective Stille coupling, where only formation of a small amount of the difuryl analog was observed. The lasts steps follows those used in the synthesis of the 1-deazapurines **5** (Scheme 1); reduction of the nitro group followed by reaction of the diamine with triethylortoformate to give the bicycle **12**. The regioselective outcome of the Stille coupling was determined by NOE spectroscopy on the diamine **11** as shown in Scheme 3.

(Scheme 3)

The bicyclic compounds **13** and **14** were attractive starting materials for the synthesis of the 1,7-dideaza- **17** and 3,7-dideazapurines **18**, since compounds **13a**, **14a**, and **14b** were commercially available (Scheme 4). Targets **17** and **18** were synthesized by N-alkylation of the pyrrole nitrogen followed by Pd-catalyzed cross coupling to introduce the furyl substituent. The 1,7-dideazapurine **15a** was not reactive under conventional Stille coupling conditions, but the target **17a** was isolated in an excellent yield when a Suzuki coupling employing the reactive catalyst $[(t\text{-Bu})_3\text{P}]_2\text{Pd}$ was performed. The analog of compound **15b** where Y = Cl (structure not shown) was essentially unreactive under both Stille and Suzuki coupling conditions, but the bromide **15b**, synthesized by alkylation of **13b**,[7] could very easily be converted to the furane **17** by a Stille coupling. The reaction was carried out at ambient temperature to avoid exchange of both halides. The target **18b** was synthesized from compound **16b** by a Stille coupling. The regioselectivity was complete, and proved by the selective NOE shown in Scheme 4 as well as by HMBC NMR spectroscopy. The conversion was moderate and 33% of the starting material **16b** was recovered.

(Scheme 4)

The benzimidazole **22** was synthesized from the commercially available nitrobenzene **19** (Scheme 5). The nitro group was conveniently reduced and the diamine **20** gave the benzimidazole **21** upon reaction with triethylorthoformate, but in contrast to similar reactions on the diaminopyridines **4** (Scheme 1) and **11** (Scheme 3). When the ring forming reaction was performed with triethylorthoformate and acetic acid anhydride, the product **21** was contaminated with ca 20% of the corresponding 3-metylbenzimidazole (structure not shown). Instead the cyclization was carried out

in the presence of *p*-toluenesulfonic acid.[8] Low reactivity of bromobenzimidazoles in Pd-catalyzed cross couplings is reported before,[9] and the final Stille coupling to give the target **22** required a reactive catalyst; $[(t\text{-Bu})_3P]_2Pd$.

(Scheme 5)

Finally the indole **25**, formally the 1,3,7-trideaza analog of the purine **1a** (Fig. 1) was synthesized by N-alkylation followed by Stille coupling, from the bromoindole **23**. Dialkylation of indoles is not uncommon,[10] and also compound **24b** was formed in the alkylation step. Due to the inactivity of the indole **25** as *Mtb* inhibitor (see below), no attempt was done to improve the outcome of the alkylation reaction.

(Scheme 6)

Biological evaluation

The target compounds **5a**, **5b**, **7**, **12**, **17a**, **17b**, **18a**, **18b**, **22** and **24** were screened for activity against *M. tuberculosis* $H_{37}Rv$ in the microplate alamar blue assay (MABA)[11] and the MIC values are given in Table 1. For compounds displaying substantial activity, cytotoxicity towards mammalian cells (VERO cells) was also examined. The values for the previously synthesized purines and deazapurines **1a** – **d** as well as a general structure of the targets, are shown in Fig. 1. The 1-deazapurines **5a** and **5b** and the 1,7-dideazapurines **17a** and **17b** possessed no significant inhibitory activity against *Mtb*, indicating that a nitrogen in the purine 1-possition may be important for binding to the (unknown) target. In contrast to earlier findings studying purines,[2] 7-deazapurine[3e] or pyrimidine[3b,3d] analogs as antimycobacterials, it is also interesting to note that this is the first time we observe that a chlorine, in what may be referred to as the 2-position in the parent purine, does not increase the antimycobacterial activity. The 3-deazapurines **7** and **12**, on the other hand, where slightly more active than the parent purines (compounds **1a** and **1b**, respectively), indicating that the purine N-3 is not involved in binding to target. The toxicity towards mammalian cells (EC_{50} VERO cells >128 μM) was also low for these compounds. In compounds **18** both the purine N-3 and N-7 is changed with CH. These modifications did not result in an additional

improvement of the activity compared to the corresponding 7-deaza- (**1c** and **1d**), but the activity is slightly increased compared to the 3-deazapurines **7** and **12**. Furthermore, the toxicity towards VERO cells was increased substantially when the N-7 nitrogen was removed. This is in accordance with what we found when we were comparing purines **1a** and **1b** with the deazapurines **1c** and **1d**.[3e] The benzimidazole **22** and the indole **25** did not exhibit significant antimycobacterial activity compared with the most active compounds in this series. The results presented herein and in our recent paper on 7- and 9-deazapurines[3e] indicate that the purine N-1 and N-9, but not N-3 and N-7, are important for binding to the elusive target. However, it must be stressed that the changes in antimycobacterial activities observed may also be a result of different uptake or metabolism by the *Mtb* cells.

A sub-population of the *Mtb* isolate in a state of non-replicating persistence (NRP). NRP is considered to be an important factor contributing to the long treatment duration (≥6 months required). Hence we investigated if the antimycobacterial purines and non-purine analogs described herein also could affect *Mtb* in NRP. Compounds **7**, **12**, and **18** were thus tested in the low-oxygen-recovery assay (LORA)[12] (Table 1). These substances (except **18b**) were all more active in the LORA assay than the purines and 7-deazapurines (MIC LORA >128 μM for all compounds **1a-d**).[3e] Unfortunately the activities found are still quite moderate. The most potent compound in the LORA assay, the 3,7-dideazapurine **18a**, is unfortunately exhibiting the highest toxicity towards VERO cells among the compounds tested for mammalian cytotoxicity.

Compounds **5a**, **5b**, **7**, **12**, **17a**, **17b**, **18a**, **18b**, **22** and **25** displayed no significant activities against *Staphylococcus aureus* and *Escherichia coli*. The MICs for all compounds were >16 μg/mL against both bacteria. There was no visible difference in the growth responses of the quality control (QC) strains across the range of dilutions tested. The $MIC_{gentamicin}$ value for the quality control strains of *S. aureus* and *E. coli* was 0.5 μg/mL which is within the acceptable specified range.[13] This points towards a selective antimycobacterial mechanism for the 3-deazapurines **7**, **12** and **18** as previously found also for purines[2] and 7-deazapurines.[3e]

(Table 1)

Experimental

The ^{1}H NMR spectra were recorded at 600 MHz with a Bruker AVII 600 instrument, at 300 MHz with a Bruker Avance DPX 300 instrument, or at 200 MHz with a Varian Gemini instrument. The decoupled ^{13}C NMR spectra were recorded at 150, 125, 75 or 50 MHz using instruments mentioned above. Mass spectra under electron impact conditions were recorded with a VG Prospec instrument at 70 eV ionizing voltage, and are presented as *m/z* (% rel. int.). Elemental analyses were performed at School of Chemistry, University of Birmingham, UK. Melting points were determined with a Büchi Melting Point B-545 apparatus and are uncorrected. Triethylamine was distilled from CaH_2 and stored over molecular sieves (3 Å). Dioxane was distilled from Na/benzophenone, *n*-butanol from BaO and acetic acid anhydride from $CaCl_2$. Dry THF and DMF were obtained from a solvent purification system, MB SPS-800 from MBraun, Garching, Germany. Silica gel for flash chromatography was purchased from Merck, Darmstadt, Germany (Merck No. 09385). All other reagents were commercially available and used as received. 4-Chloro-7-azaindole (**13a**) was purchased from Carbocore Research Chemicals and Intermediates, The Woodlands, USA; 4-chloro-1*H*-pyrrolo[3,2-*c*]pyridine (**14a**) from CreaGen Biosciences Inc, Woburn, USA; 4,6-dichloro-1*H*-pyrrolo[3,2-*c*]pyridine (**14b**) from Activate Scientific GmbH, Prien, Germany and 3-bromo-*N*-(4-methoxybenzyl)-2-nitroaniline (**19**) from Combi-Blocks, LLC, San Diego, USA. Compounds synthesized by literature procedures: **2a**,[4] **2b**,[4] **6**,[5] and **8**.[6] 4-Bromo-6-chloro-1*H*-pyrrolo[2,3-*b*]pyridine **13b** was also synthesized according to the litterature[7] and isolated as an inseparable mixture (77 : 23) of **13b** and the 4,6-dichloro analog. Activities against *Mtb* H_{37}Rv (ATCC #27294) (MABA and LORA assay),[3e,11,12] and VERO cells[2] were determined as reported before.

4-(Furan-2-yl)-*N*-(4-methoxybenzyl)-3-nitropyridin-2-amine (3a). A mixture of compound **2a** (350 mg, ca 88% pure, ca. 1.38 mmol), 4-methoxybenzylamine (0.400 mL, 3.12 mmol) and triethylamine (0.430 mL, 3.12 mmol) in *n*-butanol (10 mL) was heated at 100 ^{o}C for 18 h under N_2

and evaporated *in vacuo*. The residue was diluted with CH_2Cl_2 (ca. 10 mL) and evaporated with small amount of silica gel. The product was purified by flash chromatography on silica gel eluting with hexane followed by EtOAc-hexane (1:5) and finally EtOAc-hexane (1:4); yield 435 mg (97%), mp 119-120 ^oC, yellow solid. ^1H NMR (Me_2CO-d_6, 300 MHz) δ 3.75 (s, 3H, CH_3), 4.70 (d, J = 5.8 Hz, 2H, CH_2), 6.73 (dd, J = 3.5 and 1.7 Hz, 1H, H-4 in furyl), 6.86 (d, J = 8.7 Hz, 2H, Ar), 6.93-6.96 (m, 3H, NH, H-5 and H-3 in furyl), 7.32 (d, J =8.8 Hz, 2H, Ar), 7.73 (dd, J = 1.8 and 0.7 Hz, H-5 in furyl), 8.25 (d, J = 5.1 Hz, H-6); ^{13}C NMR (Me_2CO-d_6, 75 MHz) δ 44.9 (CH_2), 55.4 (CH_3), 110.8 (C-5), 112.8 (C-2 in furyl), 113.1 (C-4 in furyl), 114.5 (CH in Ar), 129.3 (C-3), 129.7 (CH in Ar), 132.5 (C-4 / C-1 in Ar), 132.8(C-4 / C-1 in Ar), 146.1 (C-5 in furyl), 148.6 (C-2 in furyl), 151.4 (C-2), 151.8 (C-6), 159.8 (C-4 in Ar); MS EI *m/z* (rel. %) 325 (12, M^+), 308 (95), 277 (100), 189 (30), 145 (24), 121 (70); HRMS Found 325.1063, calcd. for $C_{17}H_{15}N_3O_4$ 325.1063.

6-Chloro-4-(furan-2-yl)-*N*-(4-methoxybenzyl)-3-nitropyridin-2-amine (3b). A mixture of compound **2b** (300 mg, 1.16 mmol), 4-methoxybenzylamine (0.08 mL, 0.6 mmol) and triethylamine (0.08 mL, 0.6 mmol) in DMF (10 mL) was stirred under N_2 at ambient temperature for 24 h and poured in to water (100 mL). The resulting mixture was extracted with EtOAc (2 × 50 mL), the combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and evaporated *in vacuo*. The residue was diluted with CH_2Cl_2 (ca. 20 mL) and evaporated with small amount of silica gel. The product was purified by flash chromatography on silica gel eluting with hexane followed by CH_2Cl_2-hexane (1:4) and finally CH_2Cl_2-hexane (1:2); yield 183 mg (88%), yellow wax. ^1H NMR (MeCN-d_3, 300 MHz) δ 3.75 (s, 1H, OCH_3), 4.57 (d, J = 5.8 Hz, 2H, CH_2), 6.59 (dd, J = 3.4 and 1.7 Hz, 1H, H-4 in furyl), 6.85-6.88 (m, 3H, H-5 and CH in Ar), 6.92 (br d, J = 3.5 Hz, 1H, H- 3 in furyl), 7.00 (br s, 1H, NH), 7.28 (d, J = 8.6 Hz, 2H, CH in Ar), 7.62 (br d, J = 0.9 Hz, 1H, H-5 in furyl); ^{13}C NMR (MeCN-d_3, 75 MHz) δ 45.0 (CH_2), 55.8 (OCH_3), 110.6 (C-5), 113.3 (C-4 in furyl), 113.9 (C-3 in furyl), 114.7 (CH in Ar), 127.6 (C-3), 129.8 (CH in Ar), 131.7 (C-1 in Ar), 136.5 (C-6), 146.5 (C-5 in furyl), 147.9 (C-2 in furyl), 151.7 (C-2), 152.9 (C-6), 159.9

(C-4 in Ar), the signal from C-4 was hidden; MS EI *m/z* (rel. %) 359 (1, M^+), 344 (18), 311 (44), 223 (15), 179 (19), 121 (100), 77 (12); HRMS Found 359.0663, calcd. for $C_{17}H_{14}ClN_3O_4$ 359.0673.

4-(Furan-2-yl)-*N*^{2}-(4-methoxybenzyl)pyridine-2,3-diamine (4a). $Na_2S_2O_4$ (125 mg, 0.740 mmol) was added to a well-stirred suspension of compound **3a** (60 mg, 0.18 mmol) and K_2CO_3 (124 mg, 0.900 mmol) in MeOH (3.00 mL) and water (0.50 mL) under N_2 The resulting mixture was stirred at ambient temperature for 12 h and evaporated *in vacuo.* CH_2Cl_2 (10 mL) was added and the resulting suspension was filtered through a cotton plug. The filtrate was dried ($MgSO_4$) and evaporated *in vacuo*. The product was purified by flash chromatography on silica gel eluting with hexane followed by EtOAc-hexane (1:5); yield 50 mg (94%), pale yellow wax. ^{1}H NMR (MeCN-d_3, 300 MHz) δ 3.75 (s, 3H, CH_3), (br s, 2H, NH_2), 4.55 (d, *J* = 5.7 Hz, 2H, CH_2), (br s, 1H, NH), 6.58 (dd, *J* = 3.5 and 1.8 Hz, 1H, H-4 in furyl), 6.72-6.76 (m, 2H, H-5 and H-3 in furyl), 6.86 (d, *J* = 8.7 Hz, 2H, Ar), 7.30 (d, *J* = 8.8 Hz, 2H, Ar), 7.50 (d, *J* = 5.4 Hz, H-6), 7.62 (dd, *J* = 1.8 and 0.6 Hz, H-5 in furyl); ^{13}C NMR (MeCN-d_3, 75 MHz) δ 45.4 (CH_2), 55.7 (CH_3), 109.2 (C-3 in furyl), 111.2 (C-5), 112.4 (C-4 in furyl), 114.5 (CH in Ar), 120.1 (C-4), 126.3 (C-3), 129.7 (CH in Ar), 133.7 (C-1 in Ar), 137.0 (C-6), 143.4 (C-5 in furyl), 150.6 (C-2), 153.0 (C-2 in furyl), 159.5 (C-4 in Ar); MS EI *m/z* (rel. %) 295 (57, M^+), 136 (6), 121 (100), 78 (5), 77 (6); HRMS Found 295.1320, calcd. for $C_{17}H_{17}N_3O_2$ 295.1321.

6-Chloro-4-(furan-2-yl)-*N*^{2}-(4-methoxybenzyl)pyridine-2,3-diamine (4b). Raney Ni (ca. 100 mg, washed with methanol) was added to a solution of compound **3b** (165mg, 0.46 mmol) in MeOH (10 mL) at 0 ^{o}C, before $NaBH_4$ (35 mg, 0.92 mmol) was added. The resulting mixture was stirred at 0 ^{o}C for 10 min and at ambient temperature for 10 min in an open flask. The reaction mixture was filtered through a small celite pad, and the filtrate was evaporated *in vacuo*. The residue was dissolved in EtOAc (20 mL), washed with water (20 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated *in vacuo*. The product was purified by flash chromatography on silica gel eluting with hexane followed by EtOAc-hexane (1:4) and finally EtOAc-hexane (2:3); yield 135 mg (89%), pale yellow wax. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.71 (s, 1H, OCH_3), 4.46 (d, *J* = 5.3 Hz,

2H, CH_2), 5.16 (s, 2H, NH_2), 6.64 (dd, *J* = 3.4 and 1.8 Hz, 1H, H-4 in furyl), 6.70 (s, 1H, H-5), 6.76 (t, *J* = 5.4 Hz, 1H, NH), 6.88 (d, *J* = 8.6 Hz, 2H, CH in Ar), 6.98 (d, *J* = 3.4 Hz, 1H, H-3 in furyl), 7.28 (d, *J* = 8.5 Hz, 2H, CH in Ar), 7.79 (br d, *J* = 1.3 Hz, 1H, H-5 in furyl); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 40.3 (CH_2), 55.0 (OCH_3), 106.8 (C-5), 109.2 (C-3 in furyl), 111.8 (C-4 in furyl), 113.6 (CH in Ar), 119.3 (C-4), 124.2 (C-3), 128.9 (CH in Ar), 131.9 (C-1 in Ar), 135.0 (C-6), 142.8 (C-5 in furyl), 148.4 (C-2), 150.2 (C-2 in furyl), 158.2 (C-4 in Ar); MS EI *m/z* (rel. %) 331 / 329 (8 / 23, M^+), 208 (2), 122 (16), 121 (100), 77 (6); HRMS Found 329.0929, calcd. for $C_{17}H_{16}ClN_3O_2$ 329.0931.

7-(Furan-2-yl)-3-(4-methoxybenzyl)-3*H*-imidazo[4,5-*b*]pyridine (5a). A mixture of compound **4** (150 mg, 0.510 mmol) in triethylorthoformate (2.0 mL) and acetic anhydride (2.0 mL) was heated at reflux under N_2 for 1.5 h and evaporated *in vacuo*. The product was purified by flash chromatography on silica gel eluting with hexane followed by EtOAc-hexane (1:5) and finally EtOAc-hexane (1:4); yield 140 mg (90%), mp 105-107 ^{o}C, colorless solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.76 (s, 3H, CH_3), 5.41 (s, 2H, CH_2), 6.60 (dd, *J* = 3.4 and 1.8 Hz, 1H, H-4 in furyl), 6.85 (d, *J* = 8.7 Hz, 2H, Ar), 7.25 (d, *J* = 8.7 Hz, 2H, Ar), 7.56-7.60 (m, 2H, H-6 and H-5 in furyl), 7.66 (d, *J* = 3.5 Hz, 1H, H-3 in furyl), 8.01 (s, 1H, H-2), 8.41 (d, *J* = 5.1 Hz, H-5); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 46.8 (CH_2), 55.3 (CH_3), 112.4 (C-6 / C-4 in furyl), 112.5 (C-6 / C-4 in furyl), 114.2 (C-3 in furyl), 114.4 (CH in Ar), 127.7 (C-1 in Ar), 129.0 (C-7), 129.3 (CH in Ar), 129.7 (C-7a), 143.3 (C-2), 143.7 (C-5 in furyl), 144.7 (C-5), 147.5 (C-3a), 149.2 (C-2 in furyl), 159.6 (C-4 in Ar); MS EI *m/z* (rel. %) 305 (87, M^+), 290 (15), 153 (6), 121 (100), 77 (7); HRMS Found 305.1164, calcd. for $C_{18}H_{15}N_3O_2$ 305.1164. Anal. Found C, 71.00; H, 4.96; N, 13.72. $C_{18}H_{15}N_3O_2$ requires C, 70.81; H, 4.95; N, 13.76%.

5-Chloro-7-(furan-2-yl)-3-(4-methoxybenzyl)-3*H*-imidazo[4,5-*b*]pyridine (5b). A mixture of compound **4b** (120 mg, 0.510 mmol) in triethylorthoformate (2.0 mL) and acetic anhydride (2.0 mL) was heated at reflux under N_2 for 1.5 h and evaporated *in vacuo*. The product was purified by flash chromatography on silica gel eluting with hexane followed by EtOAc-hexane (1:4) and finally

EtOAc-hexane (2:3); yield 102 mg (83%), mp 121-122 °C, colorless crystals. ^{1}H NMR (MeCN-d_3, 300 MHz) δ 3.74 (s, 1H, OCH_3), 5.35 (s, 2H, CH_2), 6.68 (dd, J = 3.4 and 1.8 Hz, 1H, H-4 in furyl), 6.88 (d, J = 8.7 Hz, 2H, CH in Ar), 7.53 (s, 1H, H-6), 7.72-7.75 (m, 2H, H-5 and H-3 in furyl), 8.21 (s, 1H, H-2); ^{13}C NMR (MeCN-d_3, 75 MHz) δ 47.4 (CH_2), 55.8 (OCH_3), 112.2 (C-6), 113.7 (C-4 in furyl), 115.0 (CH in Ar), 116.4 (C-3 in furyl), 129.3 (C-1 in Ar), 130.0 (C-7a), 130.1 (CH in Ar), 131.7 (C-7), 145.6 (C-2 / C-5 in furyl), 145.7 (C-2 / C-5 in furyl), 146.5 (C-5), 147.9 (C-3a), 149.2 (C-2 in furyl), 160.4 (C-4 in Ar); MS EI *m/z* (rel. %) 341 / 339 (17 / 40, M^+), 122 (16), 121 (100), 78 (8), 77 (8); HRMS Found 339.0775, calcd. for $C_{18}H_{14}ClN_3O_2$ 339.0775. Anal. Found C, 63.58; H, 3.85; N, 12.37. $C_{18}H_{14}ClN_3O_2$ requires C, 63.63; H, 4.15 ; N, 12.37%.

4-(Furan-2-yl)-1-(4-methoxybenzyl)-1*H*-imidazo[4,5-*c*]pyridine (7). A mixture of compound **6** (100 mg, 0.370 mmol), Pd(dppf)Cl_2 (15 mg, 0.019 mmol) and 2-furyl(tributyl)tin (0.14 mL, 0.44 mmol) in DMF (4 mL) was stirred at 90 °C under N_2 for 18 h, and evaporated *in vacuo*. KF in MeOH (sat. sol., 10 mL) was added to the residue and the mixture stirred for 24 h. The solvent was evaporated with small amount of silica. The product was purified by flash chromatography on silica gel eluting with hexane followed by EtOAc-hexane (1:2); yield 66 mg (60%), mp 126-128° C, pale yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.77 (s, 3H, OCH_3), 5.28 (s, 2H, CH_2), 6.60 (dd, J = 3.4 and 1.8 Hz, 1H, H-4 in furyl), 6.85 (d, J = 8.7 Hz, 2H, Ar), 7.10 (d, J = 8.3 Hz, 2H, Ar), 7.10 (d, J = 5.7 Hz, 1H, H-7), 7.66 (dd, 1H, J = 0.8 and 1.7 Hz, H-5 in furyl), 7.72 (dd, 1H, J = 0.7 and 3.4 Hz H-5 in furyl); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 48.7 (CH_2), 55.3 (OCH_3), 104.2 (C-7), 112.0 (C-4 in furyl), 113.7 (C-3 in furyl), 114.6 (CH in Ar), 126.4 (C-1 in Ar), 128.7 (CH in Ar), 136.5 (C-3a), 139.5 (C-7a), 141.5 (C-4), 141.9 (C-6), 144.0 (C-2 and C-5 in furyl), 151.1 (C-2 in furyl), 159.8 (C-4 in Ar); MS EI *m/z* (rel. %) 305 (43, M^+), 122 (9), 121 (100), 77 (5); HRMS Found 305.1164, calcd. for $C_{18}H_{15}N_3O_2$ 305.1164. Anal. Found C, 70.89; H, 4.86; N, 13.58. $C_{18}H_{15}N_3O_2$ requires C, 70.81; H, 4.95; N, 13.76%.

2,6-Dichloro-*N*-(4-methoxybenzyl)-3-nitropyridin-4-amine (9). NaH (69 mg, ca 60%, ca. 1.73 mmol) was suspended in THF (4 mL) at 0 °C and a solution of compound **8** (300 mg, 1.44 mmol) in

THF (4 mL) was added dropwise under N_2 The resulting red mixture was stirred at 0 ^oC for 1 h. In another flask containing NaI (259 mg, 1.73 mmol) in THF (4 mL), was added 4-methoxybenzyl chloride (0.23 mL, 1.7 mmol) and the resulting suspension was stirred at ambient temperature under N_2 for 1 h. The benzyl halide suspension was slowly added to the compound **8** containing solution at 0 ^oC. The resulting mixture was stirred at 0 ^oC for 2 h, the ice bath was removed and the reaction was allowed to stir at ambient temperature for 14 h before the reaction mixture was poured on to ice-water (ca. 100 mL) and extracted with EtOAc (2 × 70 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$) and evaporated *in vacuo*. The product was purified by flash chromatography on silica gel eluting with hexane followed by EtOAc-hexane (1:5); yield 330 mg (69%), yellow wax. ^1H NMR (DMSO-d_6, 300 MHz) δ 3.72 (s, 3H, CH_3), 4.43 (d, J = 6.0 Hz, 2H, CH_2), 6.89-6.93 (m, 3H, H-5 and 2H in Ar), 7.25 (d, J = 8.7 Hz, 2H, Ar), 8.29 (t, J = 6.0 Hz, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 44.9 (CH_2), 55.0 (CH_3), 106.9 (C-5), 114.0 (CH in Ar), 128.3 (CH in Ar), 128.8 (C-1 in Ar), 131.5 (C-3), 141.2 (C-2), 148.7 (C-4), 149.7 (C-6), 158.5 (C-4 in Ar); MS EI *m/z* (rel. %) 329 / 327 (3 / 4, M^+), 311 (11), 309 (17), 135 (38), 121 (100), 78 (9), 77 (8); HRMS Found 327.0178, calcd. for $C_{13}H_{11}Cl_2N_3O_3$327.0177.

6-Chloro-2-(furan-2-yl)-*N*-(4-methoxybenzyl)-3-nitropyridin-4-amine (10). A mixture of compound **9** (141 mg, 0.430 mmol), $(PPh_3)_2PdCl_2$ (9 mg, 0.01 mmol) and 2-furyl(tributyl)tin (0.15 mL, 0.47 mmol) in DMF (3 mL) was stirred at ambient temperature for 1 h under N_2 and poured into water (25 mL). The resulting mixture was extracted with EtOAc (3 × 20 mL), the combined organic extracts were washed with water (40 mL) and brine (30 mL), dried ($MgSO_4$) and evaporated *in vacuo*. The residue dissolved in THF (8 mL) and KF (500 mg) was added. The resulting suspension was stirred at ambient temperature for 18 h, and evaporated with small amount of silica gel. The product was purified by flash chromatography on silica gel eluting with hexane followed by EtOAc-hexane (1:5); yield 120 mg (78%), yellow wax. ^1H NMR (DMSO-d_6, 300 MHz) δ 3.72 (s, 3H, OCH_3), 4.41 (d, J = 5.9 Hz, 2H, CH_2), 6.67 (dd, J = 3.5 and 1.8 Hz, 1H, H-4 in furyl), 6.73 (s, 1H, H-5), 6.91 (d, J = 8.7 Hz, 2H, CH in Ar), 7.07 (dd, J = 3.5 and 0.7 Hz, 1H, H-3

in furyl), 7.25 (d, J = 8.7 Hz, 2H, CH in Ar), 7.85-7.88 (m, 2H, NH and H-5 in furyl); ^{13}C NMR (DMSO-d_6, 75 MHz) 44.6 (CH_2), 55.0 (OCH_3), 105.1 (C-5), 112.4 (C-4 in furyl), 113.5 (C-3 in furyl), 114.0 (CH in Ar), 128.2 (CH in Ar), 129.2 (C-1 in Ar), 130.6 (C-3), 139.9 (C-6), 145.9 (C-5 in furyl), 148.3 (C-2 in furyl), 148.7 (C-2), 150.9 (C-4), 158.4 (C-4 in Ar); MS EI *m/z* (rel. %) 359 (3, M^+), 330 (6), 135 (6), 122 (11), 121 (100), 77 (5); HRMS Found 359.0673, calcd. for $C_{17}H_{14}ClN_3O_4$ 359.0673.

6-Chloro-2-(furan-2-yl)-*N*^{4}-(4-methoxybenzyl)pyridine-3,4-diamine (11). A suspension of compound **10** (95 mg, 0.29 mmol), K_2CO_3 (240 mg, 1.74 mmol) and $Na_2S_2O_4$ (252 mg, 1.45 mmol) in MeOH (4.0 mL) and water (0.20 mL) was stirred under N_2 at ambient temperature for 12 h before the MeOH was removed *in vacuo*. The residue dissolved in EtOAc (30 mL), washed with water (20 mL), dried ($MgSO_4$) and evaporated *in vacuo*. The product was purified by flash chromatography on silica gel eluting with hexane followed by EtOAc-hexane (1:4); yield 80 mg (93%), pale yellow wax. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.73 (s, 3H, CH_3), 4.33 (d, J = 5.5 Hz, 2H, CH_2), 5.21 (br s, 2H, NH_2), 6.23 (s, 1H, H-5), 6.59-6.61 (m, 2H, H-4 in furyl and NH), 6.81 (dd, J = 3.4 and 0.7 Hz, 1H, H-3 in furyl), 6.90 (d, J = 8.7 Hz, 2H, Ar), 7.28 (d, J = 8.6 Hz, 2H, Ar), 7.76 (dd, J = 1.7 and 0.8 Hz, 1H, H-5 in furyl); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 45.4 (CH_2), 55.0 (CH_3), 101.7 (C-5), 108.6 (C-3 in furyl), 111.5 (C-4 in furyl), 113.8 (CH in Ar), 126.7 (C-6), 128.5 (CH in Ar), 129.2 (C-2), 130.2 (C-1 in Ar), 139.1 (C-3), 142.2 (C-5 in furyl), 145.1 (C-4), 153.3 (C-2 in furyl), 158.4 (C-4 in Ar); MS EI *m/z* (rel. %) 329 (11, M^+), 330 (6), 180 (2), 122 (10), 121 (100), 77 (5); HRMS Found 329.0932, calcd. for $C_{17}H_{16}ClN_3O_2$ 329.0931.

6-Chloro-4-(furan-2-yl)-1-(4-methoxybenzyl)-1*H*-imidazo[4,5-*c*]pyridine (12). A solution of compound **11** (70 mg, 0.24 mmol) in triethylorthoformate (2 mL) and Ac_2O (2 mL) was heated at reflux for 2 h under N_2 and evaporated *in vacuo*. The product was purified by flash chromatography on silica gel eluting with hexane followed by EtOAc-hexane (3:7); yield 65 mg (79%), mp 155-157 ^{o}C, pale yellow solid. ^{1}H NMR (Me_2CO-d_6, 300 MHz) δ 3.77 (s, 3H, CH_3), 5.53 (s, 2H, CH_2), 6.68 (dd, J = 3.4 and 1.8 Hz, 1H, H-4 in furyl), 6.93 (d, J = 8.7 Hz, 2H, Ar), 7.36 (d, J = 8.7 Hz, 2H, Ar),

7.48 (s, 1H, H-7), 7.77 (dd, *J* = 1.7 and 0.8 Hz, 1H, H-5 in furyl), 7.84 (dd, *J* = 3.4 and 0.7 Hz, 1H, H-3 in furyl), 8.43 (s, 1H, H-2); ^{13}C NMR (Me_2CO-d_6, 75 MHz) 48.9 (CH_2), 55.5 (CH_3), 105.2 (C-7), 112.9 (C-4 in furyl), 115.1 (CH in Ar), 115.7 (C-3 in furyl), 128.6 (C-1 in Ar), 130.0 (CH in Ar), 137.0 (C-3a), 140.8 (C-4), 142.6 (C-7a), 143.3 (C-6), 145.2 (C-5 in furyl), 147.2 (C-2), 151.1 (C-2 in furyl), 160.7 (C-4 in Ar); MS EI *m/z* (rel. %) 341 / 339 (17 / 47, M^+), 122 (13), 121 (100), 78 (8), 77 (7); HRMS Found 339.0775, calcd. for $C_{18}H_{14}ClN_3O_2$339.0775. Anal. Found C, 63.77; H, 4.31; N, 12.31. $C_{18}H_{14}ClN_3O_2$ requires C, 63.63; H, 4.15; N, 12.37%.

4-Chloro-1-(4-methoxybenzyl)-1*H*-pyrrolo[2,3-*b*]pyridine (15a). Compound **13a** (153 mg, 1.00 mmol) was dissolved in DMF (4.0 mL) and cooled to 0 ^{o}C. NaH (ca. 60%, 44 mg, ca. 1.1 mmol) was added and reaction mixture was stirred under N_2 for 1 h before 4-methoxybenzyl chloride (0.14 mL, 1.0 mmol) was added. The resulting mixture was stirred for 19 h and evaporated *in vacuo*. Water (40 mL) was added to the residue, which was extracted with EtOAc (2 × 40 mL). The combined organic layers were washed with brine (40 mL), dried ($MgSO_4$) and evaporated *in vacuo*. The product was purified by flash chromatography on silica gel eluting with CH_2Cl_2 followed by MeOH-CH_2Cl_2 (1:19); yield 235 mg (86%), pale yellow wax. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.77 (s, 3H, OCH_3), 5.41 (s, 2H, CH_2), 6.55 (d, *J* = 3.5 Hz, 1H, H-3), 6.82 (d, *J* = 8.7 Hz, 2H, Ar), 7.09 (d, *J* = 5.2 Hz, 1H, H-5), 7.16 (d, *J* = 8.7 Hz, 2H, Ar), 7.18 (d, *J* = 3.5 Hz, 1H, H-2), 8.22 (d, *J* = 5.2 Hz, 1H, H-6); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 48.3 (CH_2), 55.7 (OCH_3), 99.1 (C-3), 114.6 (CH in Ar), 116.4 (C-5), 120.4 (C-3a), 128.8 (C-1 in Ar), 129.6 (CH in Ar), 129.8 (C-2), 136.7 (C-4), 143.3 (C-6), 159.7 (C-4 in Ar); MS EI *m/z* (rel. %) 274 / 272 (14 / 43 M^+), 122 (10), 121 (100), 78 (5); HRMS Found 272.0717, calcd. for $C_{15}H_{13}ClN_2O$ 272.0716.

4-Bromo-6-chloro-1-(4-methoxybenzyl)-1*H*-pyrrolo[2,3-*b*]pyridine (15b). Compound **13b** (80 mg, ca. 0.35 mmol, cont. ca. 0.10 mmol of 6-chloro-1*H*-pyrrolo[2,3-*b*]pyridine) was dissolved in DMF (3.0 mL) and cooled to 0 ^{o}C. NaH (ca. 60%, 22 mg, ca. 0.54 mmol) was added and reaction mixture was stirred under N_2 for 1 h before 4-methoxybenzyl chloride (0.07 mL, 0.5 mmol) was added. The reaction mixture was stirred for 1.5 h while reaching ambient temperature and quenched

by adding few drops of water. The mixture was poured into water (25 mL) and extracted with EtOAc (2 × 30 mL). The combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo*. The product was purified by flash chromatography on silica gel eluting with hexane followed by EtOAc-hexane (1:5); yield 101 mg (ca. 82% **15b** and 6% **15a**), pale yellow wax. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.76 (s, 3H, OCH_3), 5.33 (s, 2H, CH_2), 6.45 (d, J = 3.5 Hz, 1H, H-3), 6.83 (d, J = 8.6 Hz, 2H, CH in Ar), 7.11-7.15 (m, 3H, H-2 and CH in Ar), 7.28 (s, 1H, H-5); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 47.9 (CH_2), 55.3 (CH_3), 100.5 (C-3), 114.2 (CH in Ar), 118.6 (C-5), 120.6 (C-3a), 126.3 (C-4), 128.4 (C-2), 128.7 (C-1 in Ar), 129.2 (CH in Ar), 144.3 (C-6), 146.0 (C-7a), 159.4 (C-4 in Ar); HRMS Found 349.9827, calcd. for $C_{15}H_{12}BrClN_2O$ 349.9822.

4-Chloro-1-(4-methoxybenzyl)-1*H*-pyrrolo[3,2-*c*]pyridine (16a). Compound **14a** (125 mg, 0.82 mmol) was dissolved in DMF (3.0 mL) and cooled to 0 ^{o}C. NaH (ca. 60%, 43 mg, ca. 1.07 mmol) was added and reaction mixture was stirred under N_2 for 1 h before 4-methoxybenzyl chloride (0.13 mL, 0.98 mmol) was added. The reaction mixture was stirred for 1.5 h while reaching ambient temperature and quenched by adding few drops of water. The mixture was poured into water (25 mL) and extracted with EtOAc (2 × 30 mL). The combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo*. The product was purified by flash chromatography on silica gel eluting with hexane followed by CH_2Cl_2-hexane (1:1); and finally CH_2Cl_2; yield 165 mg (82%), colorless wax. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.76 (s, 3H, OCH_3), 5.22 (s, 2H, CH_2), 6.65 (d, J = 3.2 Hz, 1H, H-3), 6.83 (d, J = 8.6 Hz, 2H, Ar), 7.03 (d, J = 8.5 Hz, 2H, Ar), 7.12-7.24 (m, 2H, H-2 and H-7), 8.02 (d, J = 5.8 Hz, 1H, H-6); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 50.2 (CH_2), 55.3 (OCH_3), 101.6 (C-3), 104.9 (C-7), 114.4 (CH in Ar), 123.8 (C-3a), 127.8 (C-1 in Ar), 128.3 (CH in Ar), 129.5 (C-2), 139.7 (C-6), 141.0 (C-4), 144.0 (C-7a), 159.5 (C-4 in Ar); MS EI *m/z* (rel. %) 274 / 272 (7 / 22 M^+), 122 (10), 121 (100), 78 (6); HRMS Found 272.0716, calcd. for $C_{15}H_{13}ClN_2O$ 272.0716.

4,6-Dichloro-1-(4-methoxybenzyl)-1*H*-pyrrolo[3,2-c]pyridine (16b). Compound **14b** (200 mg, 1.07 mmol) was dissolved in DMF (4.0 mL) and cooled to 0 ^{o}C. NaH (ca. 60%, 56 mg, ca. 1.39 mmol) was added and reaction mixture was stirred under N_2 for 1 h before 4-methoxybenzyl

chloride (0.16 mL, 1.18 mmol) was added. The reaction mixture was stirred for 1.5 h while reaching ambient temperature and quenched by adding few drops of water. The mixture was poured into water (25 mL) and extracted with EtOAc (2 × 30 mL). The combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo*. The product was purified by flash chromatography on silica gel eluting with hexane followed by CH_2Cl_2-hexane (1:1); and finally CH_2Cl_2; yield 250 mg (75%), colorless wax. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.78 (s, 3H, CH_3), 5.40 (s, 2H, CH_2), 6.62 (d, J = 3.3 Hz, 1H, H-3), 6.86 (d, J = 8.6 Hz, 2H, CH in Ar), 7.03 (d, J = 8.6 Hz, 2H, CH in Ar), 7.12 (d, J = 3.3 Hz, 1H, H-2), 7.16 (br s, 1H, H-7); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 50.2 (CH_2), 55.3 (CH_3), 101.7 (C-3), 104.3 (C-7), 114.5 (CH in Ar), 123.4 (C-3a), 127.3 (C-1 in Ar), 128.4 (CH in Ar), 130.5 (C-2), 141.0 (C-6), 142.3 (C-7a / C-4), 142.4 (C-7a / C-4), 159.6 (C-4 in Ar); MS EI *m/z* (rel. %) 308 / 306 (8 / 12, M^+), 122 (10), 121 (100), 78 (5); HRMS Found 306.0327, calcd. for $C_{15}H_{12}Cl_2N_2O$ 306.0327.

4-(Furan-2-yl)-1-(4-methoxybenzyl)-1*H*-pyrrolo[2,3-*b*]pyridine (17a). To a mixture of KF (59 mg, 1.0 mmol) and bis(tri-*tert*-butylphosphine)palladium(0) (4.8 mg, 5.0 μmol) was added a solution of compound **15a** (85 mg, 0.31 mmol) in dioxane (3 mL) and the mixture was stirred at ambient temperature under N_2 for 15 min, before furan-2-boronic acid (69 mg, 0.62 mmol) was added. The resulting mixture was stirred at reflux under N_2 for 2 h before the solvent was evaporated *in vacuo*. The product was purified by flash chromatography on silica gel eluting with hexane followed by EtOAc-hexane (2:3); yield 86 mg (90%), pale yellow wax. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.76 (s, 3H, OCH_3), 5.48 (s, 2H, CH_2), (dd, J = 3.4 and 1.8 Hz 1H, H-4 in furyl), 6.82 (d, J = 8.7 Hz, 2H, Ar), 6.90 (d, J = 3.5 Hz, 1H, H-3), 7.01 (d, J = 3.4, 1H, H-3 in furyl), 7.19 (d, J = 7.6 Hz, 2H, Ar), 7.21 (d, J = 3.5 Hz, 1H, H-3), 7.38 (d, J = 5.2 Hz, 1H, H-5), 7.62 (br d, J = 1.3 Hz, 1H, H-5 in furyl), 8.34 (d, J = 5.2 Hz, 1H, H-6); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 47.8 (CH_2), 55.25 (OCH_3), 100.7 (C-3), 110.4 (C-5), 110.8 (C-3 in furyl), 112.1 (C-4 in furyl), 114.1 (CH in Ar), 115.7 (C-3a), 128.5 (C-2), 129.1 (CH in Ar), 129.2 (C-1 in Ar), 141.9 (C-6), 143.7 (C-5 in furyl), 152.2 (C-2 in furyl), 159.2 (C-4 in Ar), C-4 and C-7a were hidden; MS EI *m/z* (rel. %) 304

(100, M^+), 303 (38), 289 (13), 197 (10), 121 (99); HRMS Found 304.1209, calcd. for $C_{19}H_{15}ClN_2O_2$ 304.1212. Anal. Found C, 74.60; H, 5.35; N, 9.01. $C_{19}H_{15}ClN_2O_2$ requires C, 74.98; H, 5.30; N, 9.20%.

6-Chloro-4-(furan-2-yl)-1-(4-methoxybenzyl)-1*H*-pyrrolo[2,3-*b*]pyridine (17b). A mixture of compound **15b** (175 mg, ca. 0.410 mmol, purity see above), $(PPh_3)_2PdCl_2$ (15 mg, 0.021 mmol) and 2-furyl(tributyl)tin (0.13 mL, 0.41 mmol) in DMF (3 mL) was stirred under N_2 at ambient temperature for 40 min and poured into water (20 mL). The resulting mixture was extracted with EtOAc (3 × 20 mL), the combined organic extracts were washed with water (40 mL) and brine (30 mL), dried ($MgSO_4$) and evaporated *in vacuo*. The residue was dissolved in THF (8 mL) and KF (500 mg) was added. The resulting suspension was stirred at ambient temperature for 18 h, and evaporated with small amount of silica gel. The product was purified by flash chromatography on silica gel eluting with hexane followed by EtOAc-hexane (1:9) and finally EtOAc-hexane (1:4); yield 85 mg (60%), yellow wax. ^{1}H NMR (MeCN-d_3, 300 MHz) δ 3.73 (s, 3H, OCH_3), 5.34 (s, 2H, CH_2), 6.63 (dd, J = 3.5 and 1.8 Hz, 1H, H-4 in furyl), 6.85 (d, J = 8.8 Hz, 2H, CH in Ar), 7.16-7.20 (m, 3H, CH in Ar and H-3 in furyl), 7.40-7.41 (m, 2H, H-2 and H-5 in furyl), 7.73 (dd, J = 1.7 and 0.5 Hz, H-5 in furyl); ^{13}C NMR (MeCN-d_3, 75 MHz) δ 48.2 (CH_2), 55.8 (OCH_3), 101.2 (C-3), 110.9 (C-5), 112.2 (C-3 in furyl), 113.3 (C-4 in furyl), 114.6 (C-3a), 114.9 (CH in Ar), 129.7 (CH in Ar), 130.3 (C-2), 130.8 (C-1 in Ar), 133.1 (C-4), 145.3 (C-6), 145.4 (C-5 in furyl), 148.4 (C-7a), 151.9 (C-2 in furyl), 160.2 (C-4 in Ar); MS EI *m/z* (rel. %) 340 / 338 (18 / 51, M^+), 122 (11), 121 (100), 91 (3), 77 (4); HRMS Found 338.0822, calcd. for $C_{19}H_{15}ClN_2O_2$ 338.0822. Anal. Found C, 67.66; H, 4.55; N, 8.20. $C_{19}H_{15}ClN_2O_2$ requires C, 67.36; H, 4.46; N, 8.27%.

4-(Furan-2-yl)-1-(4-methoxybenzyl)-1*H*-pyrrolo[3,2-*c*]pyridine (18a). A mixture of compound **16a** (100 mg, 0.37 mmol) and Pd(P*t*-Bu)$_2$ (6.0 mg, 0.011 mmol) in DMF (3 mL) was stirred at ambient temperature under N_2 for 5 min before 2-furyl(tributyl)tin (0.16 mL, 0.52 mmol) was added. The resulting mixture was stirred at 85 ^{o}C for 20 h. DMF was removed *in vacuo*, the residue was dissolved in THF (4 mL) and KF (ca. 0.2 g) was added. The resulting suspension was stirred at

ambient temperature for 24 h and evaporated with small amount of silica gel. The product was purified by flash chromatography on silica gel eluting with hexane, followed by EtOAc-hexane (1:4) and finally EtOAc-hexane (1:1); yield 82 mg, (73%), pale yellow wax. ^{1}H NMR (MeCN-d_6, 300 MHz) δ 3.73 (s, 3H, OCH_3), 5.31 (s, 2H, CH_2), 6.62 (dd, J = 3.3 and 1.8 Hz, 1H, H-4 in furyl), 6.85 (d, J = 8.7 Hz, 2H, CH in Ar), 7.11-7.16 (m, 4H, H-3, CH in Ar and H-3 in furyl), 7.28 (d, J = 5.7 Hz, 1H, H-7), 7.40 (d, J = 3.3 Hz, 1H, H-2), 7.70 (br s, 1H, H-5 in furyl), 8.20 (d, J = 5.7 Hz, 1H, H-6), ^{13}C NMR (MeCN-d_6, 75 MHz) δ 50.0 (CH_2), 55.8 (OCH_3), 102.7 (C-3), 105.3 (C-7), 110.1 (C-3 in furyl), 112.7 (C-4 in furyl), 115.0 (CH in Ar), 121.5 (C-3a), 129.5 (CH in Ar), 130.3 (C-1 in Ar), 131.1 (C-2), 141.1 (C-6), 141.8 (C-7a), 143.0 (C-4), 144.4 (C-5 in furyl), 156.2 (C-2 in furyl), 160.2 (C-4 in Ar); MS EI *m/z* (rel. %) 304 (56 M^+), 122 (10), 121 (100), 78 (5); HRMS Found 304.1212, calcd. for $C_{19}H_{16}N_2O_2$ 304.1212. Anal. Found C, 74.75; H, 5.16; N, 9.21. $C_{19}H_{16}N_2O_2$ requires C, 74.98; H, 5.30; N, 9.20%.

6-Chloro-4-(furan-2-yl)-1-(4-methoxybenzyl)-1*H*-pyrrolo[3,2-*c*]pyridine (18b). A mixture of compound **16b** (150 mg, 0.49 mmol), $(PPh_3)_2PdCl_2$ (18 mg, 0.025 mmol) and 2-furyl(tributyl)tin (0.170 mL, 0.54 mmol) in DMF (3 mL) was stirred under N_2 at 60 ^{o}C for 18 h and poured into water (20 mL). The resulting mixture was extracted with EtOAc (3 × 30 mL) and the combined organic extracts were washed with water (40 mL) and brine (30 mL), dried ($MgSO_4$) and evaporated *in vacuo*. The residue was dissolved in THF (8 mL) and KF (ca. 200 mg) was added. The resulting suspension was stirred at ambient temperature for 18 h, and evaporated with small amount of silica gel. The product was purified by flash chromatography on silica gel eluting with hexane followed by CH_2Cl_2-hexane (3:7); yield 70 mg (43%), yellow wax. ^{1}H NMR (Me_2CO-d_6, 600 MHz) δ 3.74 (s, 3H, CH_3), 5.40 (s, 2H, CH_2), 6.65 (dd, J = 3.4 and 1.8 Hz, 1H, H-4 in furyl), 6.78 (d, J = 8.7 Hz, 2H, Ar), 7.14 (dd, J = 3.2 and 0.7 Hz, 1H, H-3), 7.21-7.23 (m, 3H, CH in Ar and H-3 in furyl), 7.41 (d, J = 0.7 Hz, 1H, H-7), 7.53 (d, J = 3.2 Hz, 1H, H-2), 7.80-7.81 (m, 1H, H-5 in furyl); ^{13}C NMR (Me_2CO-d_6, 150 MHz) δ 50.0 (CH_2), 55.5 (CH_3), 103.0 (C-3), 104.3 (C-7), 111.3 (C-3 in furyl), 112.6 (C-4 in furyl), 114.9 (CH in Ar), 120.9 (C-3a), 129.5 (CH in Ar), 129.8

(C-1 in Ar), 132.4 (C-2), 142.1 (C-4), 142.9 (C-6), 144.0 (C-7a), 145.0 (C-5 in furyl), 155.1 (C-2 in furyl), 160.3 (C-4 in Ar); MS EI *m/z* (rel. %) 340 / 338 (10 / 33, M^+), 122 (7), 121 (100), 78 (3); HRMS Found 338.0822, calcd. for $C_{19}H_{15}ClN_2O_2$ 338.0822. Anal. Found C, 67.35; H, 4.67; N, 8.56. $C_{19}H_{15}ClN_2O_2$ requires C, 67.36; H, 4.46; N, 8.27%.

3-Bromo-*N*^{1}-(4-methoxybenzyl)benzene-1,2-diamine (20). Compound **19** (338 mg, 1.00 mmol) was suspended in MeOH (10 mL) and K_2CO_3 (829 mg, 6.00 mmol) were added followed by $Na_2S_2O_4$ (871 mg, 5.00 mmol) and water (0.3 mL). The resulting suspension was stirred under N_2 for 36 h, additional $Na_2S_2O_4$ (871 mg, 5.00 mmol) was added and the reaction mixture was stirred for further 12 h. The mixture was evaporated *in vacuo* and the residue was partitioned between water (40 mL) and EtOAc (40 mL). The phases were separated and the aq. phase was re-extracted with EtOAc (40 mL). The combined organic layers were washed with brine (40 mL), dried ($MgSO_4$) and evaporated *in vacuo*. The product was purified by flash chromatography on silica gel eluting with hexane, followed by EtOAc-hexane (1:9); yield 230 mg (75%), pale yellow oil. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.71 (s, 3H, CH_3), 4.21 (d, J = 5.7 Hz, 2H, CH_2), 4.73 (s, 2H, NH_2), 7.73 (t, J = 5.6 Hz, 1H, NH), 6.33-6.36 (m, 2H, H-5 and H-6), 6.66 (dd, J = 6.7 and 2.6 Hz, 1H, H-4), 6.86 (d, J = 8.7 Hz, 2H, CH in Ar), 7.26 (d, J = 8.7 Hz, 2H, CH in Ar); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 46.4 (CH_2), 55.0 (CH_3), 108.1 (C-3), 109.2 (C-6), 113.66 (CH in Ar), 118.2 (C-5), 119.7 (C-4), 128.4 (CH in Ar), 131.6 (C-1 in Ar), 132.3 (C-2), 136.6 (C-1), 158.1 (C-4 in Ar); MS EI *m/z* (rel. %) 308 / 306 (15 / 16, M^+), 122 (17), 121 (100), 91 (5), 78 (9), 77 (7); HRMS Found 306.0358, calcd. for $C_{14}H_{15}BrN_2O$ 306.0368.

4-Bromo-1-(4-methoxybenzyl)-1*H*-benzo[*d*]imidazole (21). *p*-Toluenesulfonic acid monohydrate (11 mg, 0.059 mmol) was added to a solution of **20** (120 mg, 0.390 mmol) in triethylorthoformate (4.5 mL) and the resulting mixture was heated at reflux under N_2 for 2 h and excess of triethylorthoformate was removed *in vacuo*. The product was purified by flash chromatography on silica gel eluting with hexane followed by EtOAc-hexane (3:1); yield 110 mg (90%), colorless wax. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.76 (s, 3H, OCH_3), 5.26 (s, 2H, CH_2), 6.84 (d, J = 8.7 Hz, 2H, CH

in Ar), 7.05-7.11 (m, 3H, H-6 and CH in Ar), 7.20-7.24 (m, 1H, H-7), 7.44 (dd, J = 7.7 and 0.9 Hz, 1H, H-5), 7.96 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 48.8 (CH_2), 55.3 (OCH_3), 109.5 (C-7), 113.9 (C-4), 114.5 (CH in Ar), 124.0 (C-6), 125.3 (C-5), 126.8 (C-1 in Ar), 128.6 (CH in Ar), 134.4 (C-7a), 142.7 (C-3a), 143.4 (C-2), 159.7 (C-4 in Ar); MS EI *m/z* (rel. %) 318 / 316 (12 / 13, M^+), 122 (9), 121 (100), 78 (6), 77 (5); HRMS Found 316.0203, cacld. for $C_{15}H_{13}BrN_2O$ 316.0211.

4-(Furan-2-yl)-1-(4-methoxybenzyl)-1*H*-benzo[*d*]imidazole (22). A mixture of compound **21**, (90 mg, 0.25 mmol) and Pd(P*t*-Bu)$_2$ (7.0 mg, 0.013 mmol) in DMF (3 mL) was stirred ambient temperature under N_2 for 5 min before 2-furyl(tributyl)tin (0.1 mL, 0.3 mmol) was added. The resulting mixture was stirred at 85 ^{o}C for 2 h. DMF was removed *in vacuo*, the residue was dissolved in THF (4mL) and KF (ca. 0.2 g) was added. The resulting suspension was stirred at ambient temperature for 24 h and evaporated with small amount of silica gel. The product was purified by flash chromatography on silica gel eluting with hexane, followed by EtOAc-hexane (1:4) and finally EtOAc-hexane (2:3); yield 58 mg (76%), mp 99-100 ^{o}C, pale yellow crystals. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.76 (s, 3H, OCH_3), 5.29 (s, 2H, CH_2), 6.56 (dd, J = 3.3 and 1.8 Hz, 1H, H-4 in furyl), 6.84 (d, J = 8.7 Hz, 2H, Ar), 7.11 (d, J = 8.8 Hz, 2H, Ar), 7.18 (dd, J = 8.0 and 1.1 Hz, 1H, H-6), 7.24-7.28 (m, 1H, H-7), 7.50-7.52 (m, 2H, H-3 and H-5 in furyl), 7.69 (dd, J = 7.4 and 1.1 Hz, 1H, H-5), 7.97 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 48.5 (CH_2), 55.3 (OCH_3), 109.0 (C-6), 110.1 (C-3 in furyl), 111.9 (C-4 in furyl), 114.4 (CH in Ar), 117.7 (C-5), 122.6 (C-6 / C-7), 123.1 (C-6 / C-7), 127.4 (C-1 in Ar), 128.5 (CH in Ar), 134.5 (C-7a), 139.5 (C-3a), 141.8 (C-5 in furyl), 142.9 (C-2), 151.4 (C-2 in furyl), 159.5 (C-4 in Ar); MS EI *m/z* (rel. %) 304 (67, M^+), 122 (12), 121 (100), 78 (5), 77 (6); HRMS Found 304.1202, calcd. for $C_{19}H_{16}N_2O_2$ 304.1212. Anal. Found C, 74.99; H, 5.47; N, 9.27. $C_{19}H_{16}N_2O_2$ requires C, 74.98; H, 5.30; N, 9.20%.

4-Bromo-1-(4-methoxybenzyl)-1*H*-indole (24a) and 4-bromo-1,3-di(4-methoxybenzyl)-1*H*-indole (24b). 4-Bromoindole (**23**) (0.38 mL, 3.0 mmol) was added drop wise to a stirring mixture of K_2CO_3 (1.24 g, 9.00 mmol) in DMF (12 mL) under N_2 at ambient temperature. The resulting mixture was stirred for 1 h, before 4-methoxybenzyl chloride (0.81 mL, 6.0 mmol) was added drop

wise. The reaction mixture was stirred for 18 h, filtered and evaporated *in vacuo*. The products were separated by flash chromatography on silica gel eluting with EtOAc-hexane (1:20) followed by EtOAc-hexane (1:10).

24a: Yield 242 mg (26%), colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.75 (s, 3H, OCH_3), 5.21 (s, 2H, CH_2), 6.57 (d, J = 3.0 Hz, 1H, H-3), 6.81 (d, J = 8.6 Hz, 2H, Ar), 6.96-7.05 (m, 3H, Ar and indole), 7.14 (d, J = 3.0 Hz, H-2), 7.20-2.28 (m, 2H, indole); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 49.7 (CH_2), 55.3 (CH_3), 101.9 (C-3), 108.9 (C-7), 114.1 (CH in Ar), 114.8 (C-4), 122.3 (C-5 / C-6), 122.4 (C-5 / C-6), 128.1 (CH in Ar), 128.6 (C-2), 128.8 (C-1 in Ar), 129.3 (C-3a), 136.4 (C-7a), 159.1 (C-4 in Ar); MS EI *m/z* (rel. %) 317 / 315 (26 / 27, M^+), 228 (7), 197 (7), 122 (13), 121 (100), 115 (19); HRMS Found 315.0268, calcd. for $C_{16}H_{14}BrNO$ 3150259.

24b: Yield 344 mg (26%), colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.77 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.40 (s, 2H, CH_2), 5.13 (s, 2H, CH_2), 6.72 (s, 1H, H-2), 6.80-6.93 (m, 4H), 6.98-7.03 (m, 3H), 7.17-2.28 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 31.5 (CH_2), 49.5 (CH_2), 55.2 (2 × CH_3), 109.0 (C-7), 113.6 (CH in Ar), 114.0 (CH in Ar), 114.5 (C-3 / C-4), 116.1 (C-3 / C-4), 122.4 (C-5 / C-6), 123.5 (C-5 / C-6), 126.0 (C-3a), 127.8 (CH in Ar), 128.5 (C-2), 129.0 (C-1 in Ar), 129.7 (CH in Ar), 133.6 (C-1 in Ar), 137.8 (C-7a), 157.6 (C-4 in Ar), 159.0 (C-4 in Ar); MS EI *m/z* (rel. %) 437 / 435 (15 / 15, M^+), 355 (1), 316 (2), 315 (1), 235 (3), 234 (2), 192 (2), 191 (4), 190 2) 122 (9), 121 (100); HRMS Found 435.0813, calcd. for $C_{24}H_{22}BrNO_2$ 435.0834.

4-(Furan-2-yl)-1-(4-methoxybenzyl)-1*H*-indole (25). A mixture of **24a** (190 mg, 0.600 mmol), 2-furyl(tributyl)tin (0.28 mL, 0.90 mmol) and $(Ph_3P)_2PdCl_2$ (22 mg. 0.030 mmol) in DMF (5 mL) was stirred at 90 ^{o}C under N_2 for 17 h, and evaporated *in vacuo*. KF in MeOH (sat. sol., 10 mL) was added to the residue and the resulting mixture was stirred for 18 h. The product was purified by flash chromatography on silica gel eluting with EtOAc-hexane (1:10); yield 138 mg (76%), pale yellow oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.76 (s, 3H, OCH_3), 5.27 (s, 2H, CH_2), 6.53 (m, 1H, furyl), 6.79-6-84 (m, 3H, H-3 and Ar), 6.98 (d, J = 3.2 Hz, 1H), 7.06 (d, J = 8.4 Hz, 2H, Ar), 7.17-7.21 (m, 3H), 7.48 (m, 1H), 7.54 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 49.6 (CH_2), 55.1 (CH_3),

101.5 (C-3), 106.3 (C-7 / CH in furyl), 109.1 (C-7 / CH in furyl), 111.4 (C-7 / CH in furyl), 116.2 (C-5 / C-6), 121.6 (C-5 / C-6), 123.1 (C-3a / C-4), 124.2 (C-3a / C-4), 128.0 (CH in Ar), 128.6 (C-2), 129.2 (C-1 in Ar), 136.8 (C-7a), 141.5 (CH in furyl), 154.4 (C in furyl), 158.9 (C-4 in Ar); MS EI *m/z* (rel. %) 303 (100, M^+), 183 (6), 182 (6), 155 (4), 154 (5), 153 (3), 127 (6), 126 (3), 122 (10), 121 (100), 78 (6), 77 (6); HRMS Found 303.1252, calcd. for $C_{20}H_{17}NO_2$ 303.1259.

Determination of activity against *S. aureus* and *E. coli*. The antimicrobial susceptibilities of the quality control (QC) strains *S. aureus* (ATCC 29213) and *E. coli* (ATCC 25922) to test antimicrobials were determined by the broth microdilution method using cation-adjusted Mueller-Hinton broth (Oxoid, UK) essentially as previously described.[14] In brief, serial twofold dilutions (16 – 0.125 μg/mL) of all samples were prepared in triplicate in microtiter plates and inoculated with a suitably prepared cell suspension to achieve the required start concentration. DMSO was used as solvent and diluent for the test substances, whereas the gentamicin control (used to control the accuracy of testing) was prepared using water as solvent and broth as diluent. Dilution schemes, preparation of the inoculum and incubation conditions were as described in the standard method and in the performance standards supplement.[13,14] For both test substances and gentamicin the lowest concentration that completely inhibited microbial growth as detected by the unaided eyes was taken as the substance MIC value

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Legends to Figures and Schemes

Fig. 1. Structures of some of the most active purines and deazapurines **1** as well the general structure of the target compounds described in this study.

Scheme 1. (a) *p*-MeO-C_6H_4-CH_2NH_2, Et_3N, *n*-BuOH (DMF as solvent for **3b**); (b) $Na_2S_2O_4$, K_2CO_3, MeOH, H_2O, for **4a**; (c) Raney Ni, $NaBH_4$, MeOH for **4b**; (d) $CH(OEt_3)$, Ac_2O, Δ.

Scheme 2. (a) (2-Furyl)$SnBu_3$, Pd(dppf)Cl_2, DMF, 90 ^oC.

Scheme 3. (a) NaH, NaI, *p*-MeO-C_6H_4-CH_2Cl, THF, 0 ^oC – r.t.; (b) (2-Furyl)$SnBu_3$, $(Ph_3P)_2PdCl_2$, DMF; (c) $Na_2S_2O_4$, K_2CO_3, MeOH, H_2O; (d) $CH(OEt)_3$, Ac_2O, Δ.

Scheme 4. (a) NaH, *p*-MeO-C_6H_4-CH_2Cl, DMF; (b) (2-Furyl)$B(OH)_2$, [(*t*-Bu)$_3$P]$_2$Pd, KF, dioxane, Δ, for **17a**; (c) (2-Furyl)$SnBu_3$, $(Ph_3P)_2PdCl_2$, DMF, for **17b** (r.t.) and **18b** (60 ^oC); (d) (2-Furyl)$SnBu_3$, (*t*-$Bu_3P)_2$Pd, DMF, 85 ^oC, for **18a**.

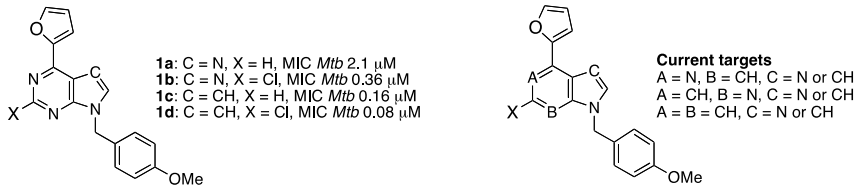
Scheme 5. (a) $Na_2S_2O_4$, K_2CO_3, MeOH, H_2O; (b) $CH(OEt)_3$, *p*-TSA, Δ; (c) (2-Furyl)$SnBu_3$, [(*t*-Bu)$_3$P]$_2$Pd, DMF, 85 ^oC.

Scheme 6. (a) K_2CO_3, *p*-MeO-C_6H_4-CH_2Cl, DMF; (b) (2-Furyl)$SnBu_3$, $(Ph_3P)_2PdCl_2$, DMF, 90 ^oC.

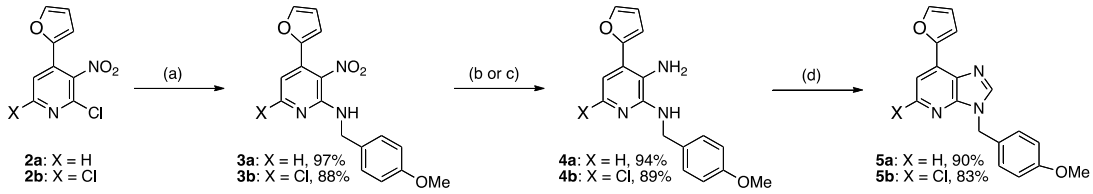
Table. Antibacterial activity against *M. tuberculosis*, and cytotoxic activity against VERO cells for compounds **5a**, **5b**, **7**, **12**, **17a**, **17b**, **18a**, **18b**, **22** and **25**.

Comp. No.	X[a]	A[a]	B[a]	C[a]	MIC (MABA) *M. tuberculosis* $H_{37}Rv$ (μM) [inhib. at 128 (μM)][b]	MIC (LORA) *M. tuberculosis* $H_{37}Rv$ pFPCA-luxAB (μM)[c]	IC_{50} VERO cells (μM) [inhib. at 128 (μM)][d]	SI (EC_{50}:MIC)
5a	H	CH	N	N	63	n.d.[e]	n.d.	n.d.
5b	Cl	CH	N	N	>128 [37%]	n.d.	n.d.	n.d.
7	H	N	CH	N	0.84	80	>128 [0%]	>150
12	Cl	N	CH	N	0.16	48	>128 [30%]	>800
17a	H	CH	N	CH	44	n.d.	n.d.	n.d.
17b	Cl	CH	N	CH	>128 [86%]	n.d.	n.d.	n.d.
18a	H	N	CH	CH	1.40	28	12	8.6
18b	Cl	N	CH	CH	0.090	>128 [53%]	58	644
22	H	CH	CH	N	29	n.d.	n.d.	n.d.
25	H	CH	CH	CH	>21 [0% at 21 μM]	n.d.	n.d.	n.d.

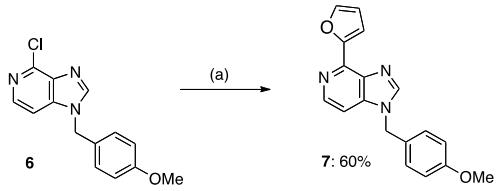
(a) See Fig. 1; (b) MIC rifampicin 0.09 μM, MIC isoniazid 0.28 μM, MIC PA-824 0.44 μM; (c) MIC rifampicin 0.97 μM, MIC isoniazid >128 μM, MIC PA-824 3.11 μM; (d) EC_{50} hyamine 0.01 μg/mL (ca. 0.03 μM); (e) Not determined.



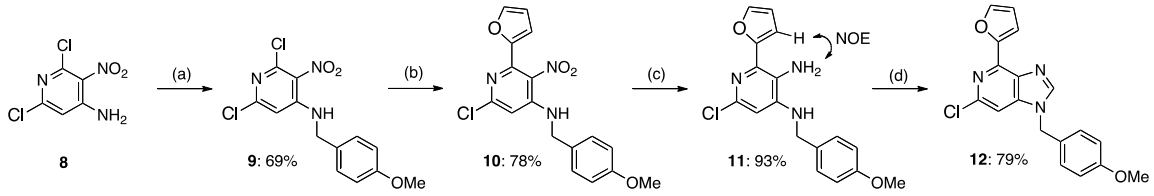
(Fig. 1)



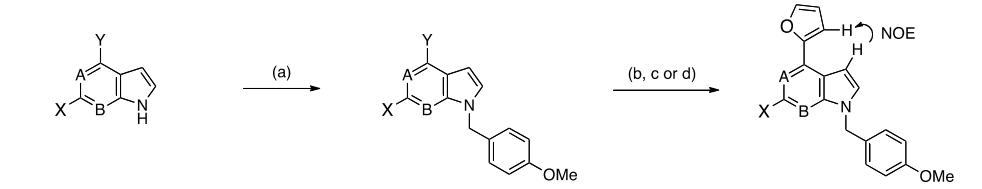
(Scheme 1)



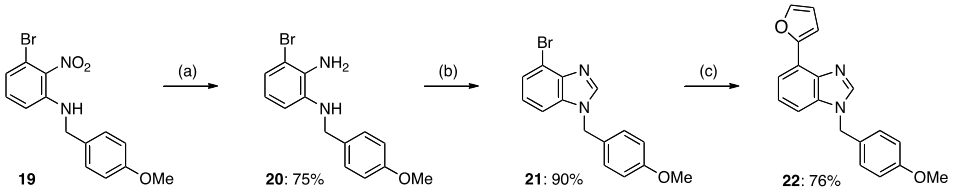
(Scheme 2)



(Scheme 3)

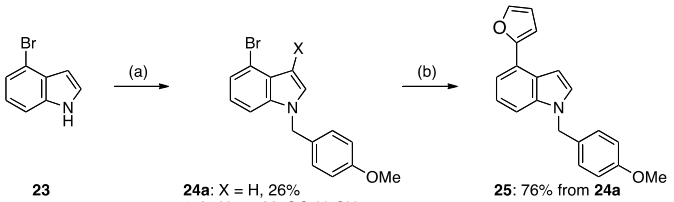


(Scheme 4)



19 **20**: 75% **21**: 90% **22**: 76%

(Scheme 5)



23

24a: X = H, 26%
24b: X = *p*-$MeOC_6H_4CH_2$, 26%

25: 76% from **24a**

(Scheme 6)